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PLASMA POTASSIUM CHANGES WITH HIGH INTENSITY EXERCISE

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SUMMARY

1. Exercise seems to change the extracellular potassium concentration far beyond the narrow limits seen in resting subjects. To examine alterations in plasma potassium concentration during exercise, twenty healthy, well-trained men ran on the treadmill at 6 deg inclination with catheters inserted in the femoral vein and artery.

2. During 1 min exhausting exercise plasma potassium concentration rose in parallel in the vein and artery, reaching peak post-exercise values of $8{\cdot}34 \pm 0{\cdot}23$ mmol l^{-1} and $8{\cdot}17 \pm 0{\cdot}29$ mmol l^{-1}. After 3 min recovery the potassium concentration was $0{\cdot}50 \pm 0{\cdot}05$ mmol l^{-1} below pre-exercise values. Both the rise of plasma potassium concentration during exercise and the decline during recovery followed exponential time courses with a half-time of 25 s.

3. Exercise at reduced intensity showed that the peak post-exercise potassium concentration was linearly related to the exercise intensity. Individual resting, peak and nadir values were proportionally related.

4. The increased potassium concentration during exercise can be explained in full by the electrical activity in the exercising muscles. Repeated 1 min exhausting exercise bouts revealed no relationship between potassium concentration and plasma pH nor glycogen break-down.

5. All of the observations fit a simple model of potassium efflux from active muscle and elimination from blood with the following characteristics: the efflux increases (decreases) stepwise at the onset (end) of exercise, and the efflux rate during exercise increases with exercise intensity. Potassium is eliminated from blood by a proportional regulator which may be the Na^+–K^+ pump of the exercising muscle. Extracellular potassium is indirectly linked to the pump stimulus, and the rate of reuptake is proportional to the extracellular accumulation. Thus no limited maximal power for potassium uptake was found. The post-exercise undershoot of 0·5 mmol l^{-1} can be explained by a higher gain of the pump after exercise.

6. The large, rapid changes in the plasma potassium concentration during and after exercise is due to the first order kinetics of the reuptake mechanism rather than to a limited power to take up potassium.

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INTRODUCTION

Exercise causes skeletal muscle to lose potassium which during short-lasting bouts will accumulate in the extracellular space. The increase of plasma potassium concentration occurs rapidly at the onset of activity, and the excess potassium is cleared again when exercise ceases (Carlsson, Fellenius, Lundborg & Svensson, 1978; Hirche, Schumacher & Hagemann, 1980; Sejersted, Medbø, Orheim & Hermansen, 1984). The increased potassium efflux from exercising muscles is most likely due to the increased electric activity in the muscle cells (Fenn, 1938).

The tight regulation of plasma potassium concentration in the resting condition may seem to be disrupted during exercise. The exact nature and regulation of the processes that cause potassium release and reuptake are still far from clear. We hypothesized that the changes in plasma potassium concentration can be modelled as follows: at the onset of exercise there is a stepwise increase in the potassium efflux which is compensated for by a gradual activation of a reuptake as the extracellular potassium concentration rises. Provided the reuptake mechanism has a sufficient power, a new steady-state level will be reached if the uptake is stimulated enough. At the termination of exercise the potassium release is probably suddenly reduced. The fall in the plasma potassium concentration after exercise will therefore provide information about the reuptake mechanisms clearing potassium from plasma.

The present study is aimed at testing various experimental exercise conditions in human subjects that might affect the rate and magnitude of changes in plasma potassium concentration. The observations are compared with the predictions of the model.

Provided muscle potassium release during exercise is caused by the increased electric activity in the muscles (Fenn, 1938), the extracellular potassium concentration can be expected to increase with exercise duration and intensity. Peak values are possibly reached during exhausting exercise.

Since there may be a relationship between muscle potassium and glycogen (Ahlborg, Bergström, Ekelund & Hultman, 1967), it was ascertained that glycogen break-down is not a significant cause of increased extracellular potassium concentration. Furthermore, potassium may be exchanged with hydrogen ions during acidosis (Burnell, Villamil, Uyeno & Scribner, 1956), and the relationship between plasma potassium concentration and pH was examined during repeated bouts of exercise.

METHODS

Subjects

Twenty subjects participated in the studies, and detailed characteristics of the subjects have been given previously (Hermansen, Orheim & Sejersted, 1984; Medbø & Sejersted, 1985). Ten of the subjects were endurance-trained (ET, cross-country skiers, and marathon runners with a best time of 135–160 min). The endurance-trained subjects were 27 ± 1 years old (range: 20–33 years) and $1{\cdot}82 \pm 0{\cdot}02$ m tall (1·72–1·91 m), weighed 69 ± 2 kg (61–82 kg), and had a maximal oxygen uptake of 52 ± 1 μmol kg^{-1} s^{-1} (46–58 μmol kg^{-1} s^{-1}). The other ten subjects were sprint-trained (ST, 200–800 m track running with best time on 400 m of 47–52 s). They were 23 ± 1 years old (18–33 years) and $1{\cdot}82 \pm 0{\cdot}02$ m tall (1·73–1·95 m), weighed 72 ± 3 kg (61–88 kg), with a maximal oxygen uptake of 47 ± 1 μmol kg^{-1} s^{-1} (42–52 μmol kg^{-1} s^{-1}). Twelve of the subjects (six ET and six ST) participated in series 1 (see below) with one exhausting 1 min exercise bout, while the other

eight (four ET and four ST) participated in series 3 with five exhausting bouts. Eight of the subjects (four ET and four ST) taking part in series 1 also participated, partly or fully, in series 2.

The protocol of the experiments and the procedures used were approved by the Ethics Committee at the Department of Physiology, National Institute of Occupational Health.

Procedures

All experiments were done on a motor-driven treadmill at 6 deg (10·5%) inclination. The subjects were fully informed about the experimental procedures before they gave their written consent. They underwent a medical examination and were trained in treadmill running. The maximal oxygen uptake was measured, and the highest speed each subject could keep for 1 min was established. For the subjects in series 3 the speed was reduced by 8% so that they were able to endure the first two bouts for 60 s (see below).

On the day of the experiment the subjects arrived at the laboratory in the morning after an overnight fast. Polyethylene catheters were inserted into the right femoral artery and vein, and blood was thus sampled from veins draining the exercising muscles. The subjects warmed up for 10 min at a speed corresponding to 50% of their maximal oxygen uptake, which did not change blood pH or lactate concentration, followed by a 10 min pause. In series 1 the subjects ran for 1 min to exhaustion. In series 3 the subjects ran five times for a maximum of 1 min or until exhaustion. The five bouts were separated by 4 min rest. After 1 h 40 min rest some of the subjects taking part in series 1 did four more runs (series 2), first for 1 min at 40 and 70% of the treadmill speed causing exhaustion in 1 min ($n = 8$). Thereafter they exercised for 24 and 42 s at the intensity leading to exhaustion in 1 min ($n = 6$). The speeds and durations were selected so that the distances covered in both cases were exactly 40 and 70% of the distance they ran during the 1 min exhausting bout in series 1. There was a 15 min pause between each of the four bouts of exercise in series 2.

In series 1 and 2 blood samples for determination of plasma potassium concentration were taken just before exercise (10 min after the warming-up), two were taken immediately after exercise (about 10 and 20 s respectively), and single samples were taken at 1, 3, 6 and 9–10 min post-exercise. In addition the plasma potassium concentration was measured 30 s and 60 min post-exercise in series 1. In series 1 both arterial and femoral–venous blood samples were taken, in series 2 only femoral–venous samples. In series 3 one blood sample was taken before each exhausting bout, and two samples were taken immediately after ($\approx$ 10 and 20 s respectively). In the recovery after the fifth bout additional blood samples were taken 5, 10, 20, 30, 40, 50 and 60 min post-exercise. From all samples in series 3 both arterial and femoral–venous blood pH and plasma potassium concentration were measured.

Blood samples were obtained with 2 ml syringes filled with 75 μl of heparin (375 IU). The syringes were kept at 0 °C until further handling. Samples for measurement of the plasma potassium concentration were centrifuged for 8 min at 1000 *g* less than 10 min after collecting the sample. The plasma was kept frozen until the potassium concentration was measured. Blood pH was measured within 2 h. The catheters were repeatedly flushed with a heparinized isotonic glucose solution. When both arterial and femoral–venous blood samples were taken (series 1 and 3), the samples were drawn simultaneously. No correction was made for the dilution due to heparin in the syringes ($\approx$ 4%). Some samples had to be excluded due to blood coagulation or to visible haemolysis. In a control experiment we established a dilution series for haemolysed blood in plasma, and this showed that visual inspection of the plasma allowed detection of haemolysis of less than 0·05% of the red blood cells, which would increase the plasma potassium concentration by less than 0·05 mmol l^{-1}.

Methods

The maximal oxygen uptake was measured by the levelling-off criterion (Hermansen, 1974). Plasma potassium concentration was measured by flame photometry (IL 343, Instrumentation Laboratories, Lexington, MA, USA) using lithium as internal standard. Blood pH was measured on an IL 613 pH and Blood Gas Analyzer (Instrumentation Laboratories, Lexington, MA, USA).

Statistics and calculations

Data are expressed as means $\pm$ S.E.M. of individual results. Tests of statistical significance (one-tailed or two-tailed whenever appropriate) were done using Student's matched-pair test (within

groups) and Student's two-sample test (between ET and ST subjects), except for tests of the time constants. The distributions of these time constants were asymmetric but with similar variances; differences were accordingly tested by Mann–Whitney's test for two-sample and Friedman's rank test for repeated comparisons (Owen, 1962). Correlations are expressed by Pearson's correlations coefficient. The regression coefficients of linear and logarithmic curve fits were calculated by standard least-square methods, and the scatter around the fitted curves ($S_{y \cdot x}$) is used as a measure of the goodness of the fit. The level of statistical significance for the t tests was calculated by Asyst (MacMillan Software Co., Rochester, NY, USA).

The only statistically significant difference with regard to single measurements of the plasma potassium concentration between the two groups of subjects in series 1 and 2 was found 60 min after exercise in series 1. The sprint-trained and endurance-trained subjects have therefore been treated as one group in series 1 and 2.

Immediately before each blood sample taken, 0·5 ml was drawn into a separate syringe to remove the isotonic glucose flush solution in the catheters. For the samples taken immediately after exercise there was no time for this procedure, and the plasma was therefore diluted by the flush solution in the catheters. The potassium concentration in these samples has therefore been corrected for this dilution, 17% for the arterial and 25% for the femoral–venous samples.

The rate constant of an exponential levelling off can be estimated by simple least-square methods if the steady-state level is known, while the steady-state level can easily be estimated by linear regression if the rate constant is known. After exercise a steady-state level was reached, and the rate constant was therefore calculated by linear regression on the log-transformed data. No steady-state level was reached during exercise, but since both the muscle mass and the distribution volume of extracellular potassium were the same during and after exercise, we used the same rate constant in both situations. The other two regression parameters were calculated by linear regression.

The gross amount of potassium leaving the muscles due to electric activity in the sarcolemma was calculated as:

$$\{K^+\}_{pl} = ncmU/F, \tag{1}$$

where $\{K^+\}_{pl}$ is the amount of potassium leaving the muscle cells, n the number of action potentials, m the muscle mass engaged, U the voltage change during one action potential and F is Faraday's constant for conversion between charge and molar amounts. c, the specific capacitance of muscle cells, is around 4 mF kg^{-1} wet weight muscle and varies little with cell size (Westgaard, 1975; Dulhunty, Carter & Hinrichsen, 1984).

RESULTS

One minute exhausting exercise (series 1)

During the 1 min exhausting exercise arterial and femoral–venous plasma potassium concentrations rose 4·3 ± 0·2 and 4·5 ± 0·2 mmol l^{-1}, which means that the values more than doubled during the exhausting bout (Fig. 1, Table 1). Both arterial and femoral–venous plasma potassium concentrations decreased exponentially with a half-time ($t_{1/2}$) of 24·6 ± 1·6 s (Fig. 2), and the values were 0·50 ± 0·05 mmol l^{-1} below pre-exercise level between 3 and 9 min after exercise ($P < 0·001$). A best fit to the observations post-exercise was obtained by the following equation:

$$[K^+]_{pl} = 3·3 + 6·4 \exp(-0·028\, t), \tag{2}$$

for $t \geqslant 10$ s ($n = 44$, $r = -0·92$), where $[K^+]_{pl}$ is the plasma potassium concentration in mmol l^{-1} and t the time in seconds. Assuming an even distribution of potassium within a plasma volume of 3 l and within the interstitium of the exercising muscles of roughly 2 l allows an estimate of the extracellular potassium accumulation in the range of 20–30 mmol. This is a minimum estimate since the potassium probably also to some extent was distributed to the interstitial space of other tissues.

There was a positive correlation between the pre-exercise, resting plasma potas-

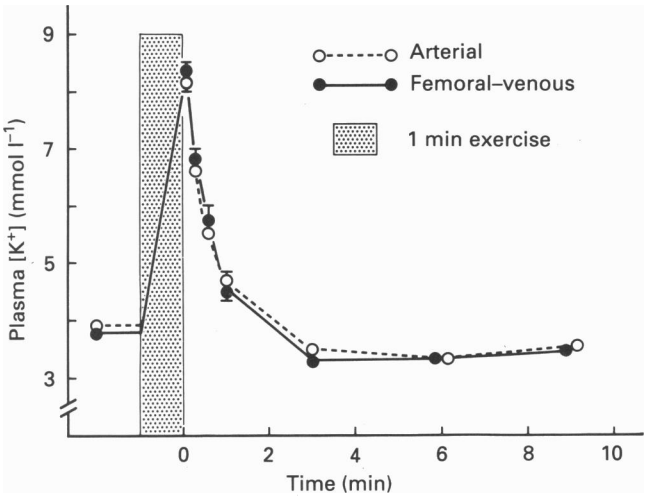

Fig. 1. Arterial and femoral–venous plasma potassium concentration before and after 1 min exhausting exercise (series 1; means ± S.E.M., $n = 12$).

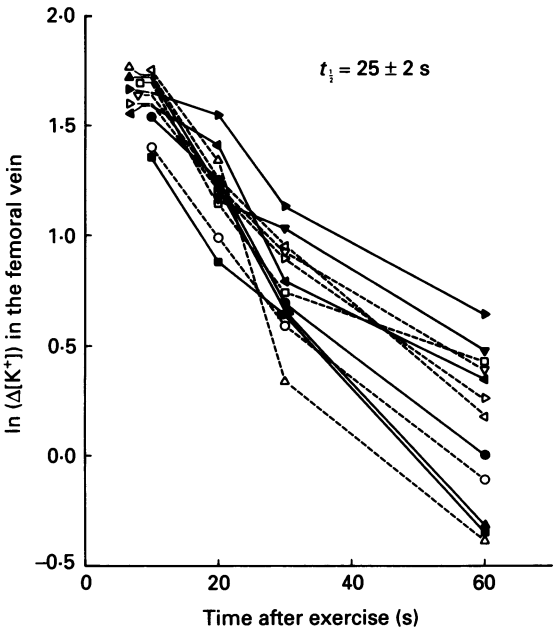

Fig. 2. Semilogarithmic plot of the femoral–venous plasma potassium concentration minus the steady-state value found 3–9 min after exercise, as a function of time. The data are from twelve subjects running to exhaustion in series 1.

TABLE 1. Summary of the main results from the three experimental series comprising running time, relative speed and femoral–venous and arterial plasma potassium concentrations

Series No.	n	Relative speed (%)	Time (s)	Distance run (m)	Plasma potassium concentration (mmol l^{-1}) Femoral–venous Pre-exercise	Femoral–venous Peak	Femoral–venous Nadir	Arterial Peak
1	12	100	60	302±9	3·80±0·06	8·34±0·23	3·33±0·07	8·17±0·29
2	8	70	60	216±8	3·80±0·10	6·39±0·24	3·51±0·10	—
2	8	40	60	124±4	4·10±0·11	5·49±0·12	3·71±0·06	—
2	6	100	42	220±9	3·50±0·05	7·38±0·21	3·17±0·11	—
2	6	100	24	126±5	3·66±0·10	6·52±0·10	3·33±0·06	—
3*	8	92	60	316±7	3·83±0·08	7·73±0·26	3·22±0·08	7·50±0·14

* First bout only. Values are means±S.E.M. n is number of subjects. A relative speed of 100% leads to exhaustion in 1 min.

TABLE 2. Speed, duration of each of the five bouts, and the total distance run in series 3

	Speed (m s^{-1})	Duration of each bout (s) 1	2	3	4	5	Sum	Total distance run (m)
Endurance-trained	5·00±0·15	58·4±1·7	56·6±2·4	55·8±2·4	46·4±2·6	39·7±2·6	256·8±4·8	1286±60
Sprint-trained	5·55±0·07	60·0±0·0	58·8±1·3	35·3±1·4	34·7±0·6	33·6±2·3	222·3±1·6	1232±8

Data are means±S.E.M. (n = 4).

sium concentrations and peak post-exercise concentrations ($r = 0{\cdot}66$, $P = 0{\cdot}015$), and also between the resting and nadir post-exercise values ($r = 0{\cdot}77$, $P = 0{\cdot}008$; Fig. 3). The regression curves did not have intercepts different from zero, which means that with 1 min exhausting exercise the plasma potassium concentra-

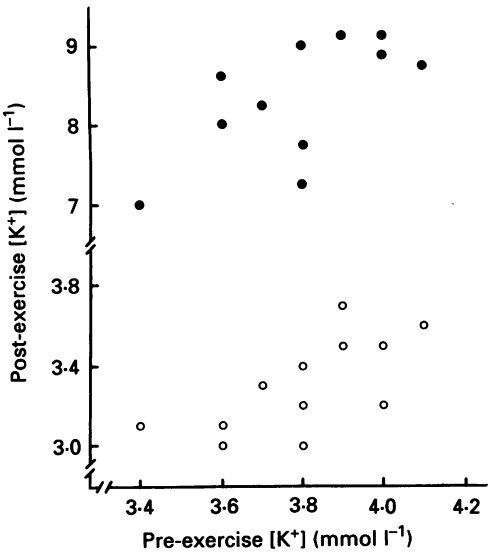

Fig. 3. Plasma potassium concentration immediately after (peak, ●, $r = 0{\cdot}66$) and 3–9 min after (nadir, ○, $r = 0{\cdot}77$) exercise *versus* pre-exercise potassium concentration in series 1 (1 min exhausting exercise, $n = 12$).

tion increased $120 \pm 5\%$ independently of the starting level and subsequently fell $60{\cdot}7 \pm 0{\cdot}9\%$ from the peak value to $13 \pm 1\%$ below pre-exercise level. This means that subjects with the highest resting concentrations reached the highest peak and nadir values and showed the greatest fluctuations of the plasma potassium concentration in absolute terms.

No statistically significant differences between arterial and femoral–venous plasma potassium concentration could be seen. However, it would require only 2 s imprecision in the temporal matching of the sampling to mask an arterio-venous difference during the fast decrease of 1·2 mmol l^{-1} between 10 and 20 s after exercise. This precise temporal matching was impossible. The large perfusion at the end of exercise may therefore have prevented detection of a significant reuptake. This conclusion is supported by a recent study showing a significant uptake by the quadriceps muscle immediately after exercise (Juel, Bangsbo, Graham & Saltin, 1989).

The plasma potassium concentration 1 h after exercise was $3{\cdot}75 \pm 0{\cdot}08$ mmol l^{-1} for the endurance-trained and $4{\cdot}22 \pm 0{\cdot}06$ mmol l^{-1} for the sprint-trained subjects, which was close to pre-exercise values.

Graded exercise (series 2)

Additional experiments were carried out to examine the effect of reduced treadmill speed or exercise duration. One minute exercise at reduced *intensity* still increased the plasma potassium concentration during exercise, and an undershoot to below pre-exercise values was seen after exercise (Fig. 4*A*, Table 1). The hyperkalaemia at the end of exercise as well as the degree of hypokalaemia in the recovery increased roughly linearly with intensity (Fig. 5*A*).

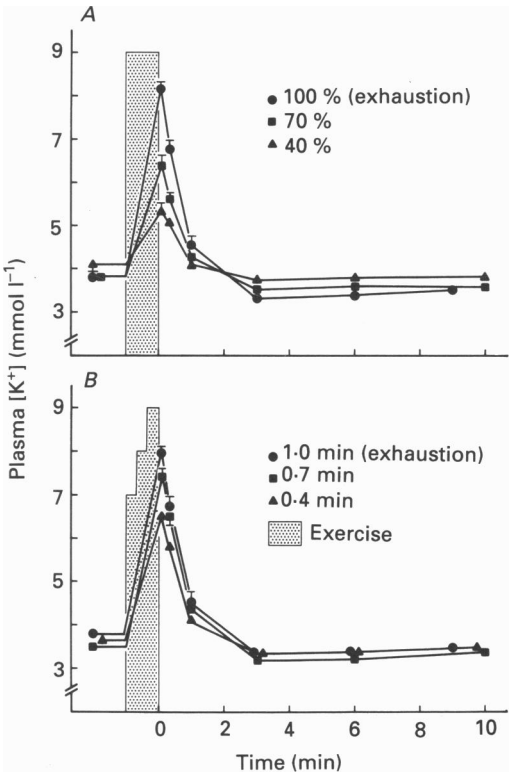

Fig. 4. Plasma potassium concentration before and after 1 min run at different intensities (*A*, $n = 8$), and runs of different durations at 100% intensity (*B*, $n = 6$) (series 2; means ± S.E.M.).

The time course of plasma potassium concentration during a 1 min run was examined by carrying out two additional runs. The treadmill speed was the same as the one leading to exhaustion in 60 s, but the *duration* was reduced to 24 s (0·4 min) and 42 s (0·7 min). The peak femoral–venous plasma potassium concentration increased exponentially with duration (Figs 4*B* and 5*B*). A significant post-exercise hypokalaemia was seen after all bouts.

Exactly the same distance was covered during the 24 s bout at full intensity as during the 1 min bout at 40% intensity. The same was true for the 42 s bout at full intensity and the 1 min bout at 70% intensity. In spite of this the plasma potassium concentration at the end of exercise was $0{\cdot}87 \pm 0{\cdot}07$ mmol l^{-1} larger ($P < 0{\cdot}001$) for

the 24 and 42 s bouts at full intensity compared with the concentrations for the matched 1 min bouts at reduced intensity. In addition the 24 and 42 s bouts at 100% intensity caused a more pronounced hypokalaemia in the recovery after exercise ($P < 0{\cdot}001$).

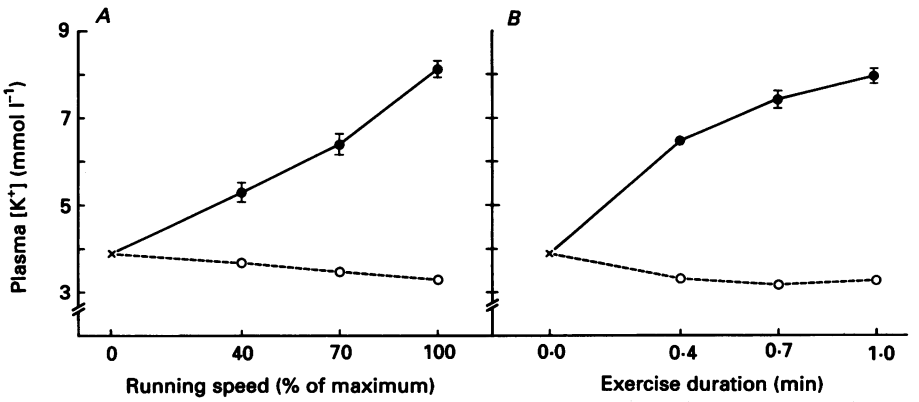

Fig. 5. The highest (10 s, ●) and lowest (3 min, ○) post-exercise plasma potassium concentrations against 1 min running at different intensities (A, $n = 8$), and running at 100% intensity for different durations (B, $n = 6$) (series 2; means ± S.E.M.). ×, pre-exercise.

All the single data of the potassium concentration during exercise both at 100% speed of different durations and for 1 min at different intensities can be fitted into one single equation:

$$[K^+]_{pl} = 3{\cdot}8 + 5{\cdot}3\, v_r(1 - \exp(-0{\cdot}0283\, t)), \quad (3)$$

($n = 49$, $r = 0{\cdot}96$, $S_{y\cdot x} = 0{\cdot}5$ mmol l^{-1}). $[K^+]_{pl}$ is the femoral–venous plasma potassium concentration in mmol l^{-1}, v_r the speed relative to the speed causing exhaustion in 1 min, t the exercise duration in seconds and $S_{y\cdot x}$ the scatter (SD) around the fitted curve. This relationship was calculated on the basis that the plasma potassium concentration increases linearly with intensity and exponentially with duration (Fig. 5A and B). As explained in the Methods the rate constant of the exponential levelling off was assumed to be the same as the rate constant for the exponential decline of the plasma potassium concentration after exercise (see below). In none of the experiments in series 1 and 2 did the measured plasma potassium concentration differ significantly from the values estimated by the above equation.

After all exercise bouts the plasma potassium concentration in the femoral vein fell monoexponentially. The half-time for the different bouts varied between $23{\cdot}7 \pm 0{\cdot}5$ and $26{\cdot}7 \pm 2{\cdot}1$ s ($P = 0{\cdot}32$). On average, therefore, for all exercise bouts the femoral–venous potassium concentration after exercise fell exponentially with a half-time of $24{\cdot}6 \pm 0{\cdot}9$ s ($n = 40$). The implication of the constant half-time in all experiments is that the rate of decline in the potassium concentration is proportional to the deviation in the peak concentration at the end of exercise from its lowest post-

exercise value. Since the slope of the relationship was $-0{\cdot}0283\ s^{-1}$, the clearance was at least $0{\cdot}14\ l\ s^{-1}$ or $8{\cdot}5\ l\ min^{-1}$, assuming a distribution volume of 5 l.

Repeated exhausting bouts of exercise (series 3)

The subjects in this series exercised 5 × 1 min to exhaustion with 4 min rest separating the exercise bouts. The plasma potassium concentration rose 3·6–3·8 mmol l^{-1}, a

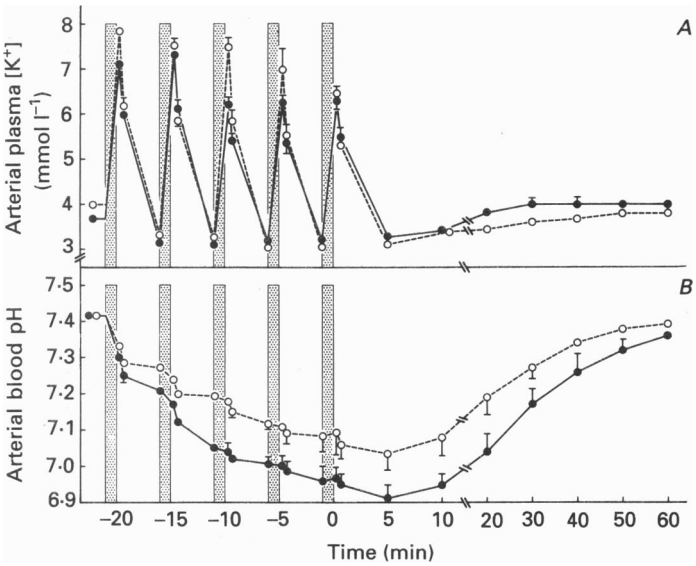

Fig. 6. Arterial plasma potassium concentration (*A*) and pH (*B*) for endurance-trained (○, $n = 4$) and sprint-trained (●, $n = 4$) subjects before and immediately after each of five successive exhausting bouts of exercise separated by 4 min rest (series 3, means ± S.E.M.). Stippled bars, 1 min exhausting exercise.

doubling for both groups during the first and second bouts ($P < 0{\cdot}001$, Fig. 6*A*). During the third, fourth and fifth bouts the two groups differed. The plasma potassium concentration for the sprint-trained subjects rose about 2·4 mmol l^{-1} (63 %) above pre-exercise values during each of the last three bouts, and this increase was less than during the first two bouts ($P < 0{\cdot}02$). For the endurance-trained subjects the hyperkalaemia at the end of the last three bouts decreased stepwise to the same level as for the sprint-trained subjects. The gradual decline of the peak post-exercise concentration might be explained by the reduced duration of the bouts (Table 2). This is supported by a good fit of the single measurements of all subjects to the equation:

$$[K^+]_{pl} = 3{\cdot}8 + 4{\cdot}8(1 - \exp(-0{\cdot}0282\,t)), \quad (4)$$

($n = 42$, $r = 0{\cdot}92$, $S_{y \cdot x} = 0{\cdot}6$). $[K^+]_{pl}$ is the plasma potassium concentration in mmol l^{-1}, t the time in seconds and $S_{y \cdot x}$ the scatter around the fitted curve. The Y-intercept of 3·8 mmol l^{-1} is the same as in eqn (3), and the slope of 4·8 mmol l^{-1} is 90 % of the slope of 5·3 mmol l^{-1} in eqn (3). This means that eqn (4) is identical to eqn (3) using a relative speed (v_r) of 0·9. Thus the two experimental series give almost identical results since the chosen speed in series 3 was 92 % of the speed causing exhaustion

in 1 min. We therefore conclude that the effect of intensity and duration on the plasma potassium concentration was the same in these subjects suffering from a gradually developing acidosis and fatigue as for the subjects in series 1 and 2.

The correlation coefficients of the fitted curves from eqns (2), (3) and (4) show that 85% or more of the variance in the individual plasma potassium concentrations was related to the exercise intensity, duration or recovery time. The residual variance is a combined effect of between-subject variation, random variation and a possible bias in the fitted curves. The effect of the first two components is reduced on mean values. The eqns (2), (3) and (4) were therefore recalculated using the mean values. The new regression coefficients were the same, and the correlation coefficients were 0·99 or better, corresponding to a scatter around the fitted curves of 0·05 mmol l^{-1}. This excludes a large bias in the models used.

Arterial blood pH and plasma potassium concentration (series 3)

The plasma potassium concentration fluctuated between supra- and subnormal values during each of the five exercise/recovery cycles. Blood pH, on the other hand, decreased steadily both during exercise and in the pauses between (Fig. 6*B*), reaching the lowest values of $7{\cdot}04 \pm 0{\cdot}05$ for the endurance-trained and $6{\cdot}91 \pm 0{\cdot}04$ for the sprint-trained subjects (0·39 and 0·50 below pre-exercise values) 5 min after the end of the fifth bout. Hence, there was no relationship between the plasma potassium concentration and blood pH.

DISCUSSION

The main result of the present study was the doubling of both the arterial and the femoral–venous plasma potassium concentrations during exhausting running. Terminating the exercise before exhaustion resulted in smaller increases. Within 3 min after exercise the hyperkalaemia was reverted to a hypokalaemia which was sustained for several minutes. The hyperkalaemia was not related to acidosis.

Causes of rise in plasma potassium concentration

The rise in the plasma potassium concentration occurring during exercise is entirely due to release from skeletal muscle (Fenn, 1938; Hnik, Holas, Krekule, Kriz, Mejsnar, Smiesko, Ukec & Vyskočil, 1976). The release has been connected to (1) propagation of action potentials, (2) intracellular acidosis, (3) glycogen break-down, (4) osmotic regulation and (5) release from red blood cells or cell damage. Previous investigations, some of which date from the 1930s, conclude that potassium release from active muscle cells is caused by local electric events (Fenn, 1938; Hnik *et al.* 1976; Hazeyama & Sparks, 1979). Isolated muscles release potassium during stimulation (Hirche *et al.* 1980), and when smaller muscle groups with intact perfusion are activated *in vivo*, a negative arterio-venous difference can be clearly demonstrated (Sjøgaard, 1986; Juel *et al.* 1989). Also, the intact non-ischaemic heart transiently releases potassium during increments in heart rate, although the amount is too small to affect the plasma concentration of mixed venous blood (Ilebekk, Andersen & Sejersted, 1986). The following calculations show that repolarizing the muscle fibres requires a potassium efflux which is so large that with 1 min exercise

the rise in the plasma potassium concentration would greatly exceed the observed values, provided all the released potassium ions were accumulated in the extracellular space. We assume an electric capacitance of 4 F kg^{-1} muscle (Westgaard, 1975; Dulhunty *et al.* 1984). If the voltage across the sarcolemma changes 0·1 V during each action potential and if 20 kg muscle is used (Bonde-Petersen, Henriksson & Lundin 1975; Sahlin, Ren & Broberg, 1988), a charge of 8 C or 8×10^{-5} mol potassium escapes the muscles during one action potential. During 1 min strenuous exercise about 1000 action potentials may be passed, giving an estimated gross efflux of 80 mmol potassium. This is at least three times more than the minimum we consider compatible with a rise in the arterial potassium concentration of 4·3 mmol l^{-1}. In addition the charge carried by potassium may be larger since we have not taken into account that the inward sodium current may overlap the outward potassium current. Therefore, the observed rise in the plasma potassium concentration can be explained in full by excitatory events in the working muscles.

The present investigation also strongly supports that acidosis or glycogen breakdown is of little or no importance for the rise of the plasma potassium concentration during exercise or recovery. The 1 min run at 40% intensity caused a significant increase in plasma potassium concentration, but exercise at this intensity and duration is not associated with changes in pH or glycogen. During the repeated bouts of exercise arterial blood pH decreased steadily, whereas the potassium concentration fell from levels above 6 mmol l^{-1} after the end of exercise to less than 3·5 mmol l^{-1} prior to the next bout. Admittedly, intracellular pH might recover to some extent during the 4 min rest periods, but a significant intracellular acidosis prevails (Hermansen & Osnes, 1972). Glycogen will be consumed during each exercise bout, and insignificant resynthesis can occur in 4 min (Hermansen & Vaage, 1977). Hence, after this kind of exercise glycogen stores in the *vastus lateralis* muscle are reduced by at least 40 mmol kg^{-1} wet weight muscle (Hermansen & Vaage, 1977). These reduced intracellular glycogen levels did not change the time course of plasma potassium concentration during exercise (see eqn (4)).

Transmembrane potassium fluxes are associated with fast cell volume regulation (Grinstein, Rothstein, Sarkadi & Gelfand, 1984). Moreover, there is strong evidence that during repeated bouts of exercise as in series 3 the cells take up fluid during exercise and release it to the interstitial space in the pauses between each bout (Sejersted, Vøllestad & Medbø, 1986). If these fluid flows were caused by potassium movements, potassium would be expected to move in parallel with water across the cell membrane. However, potassium and water moved in opposite directions, and the osmotic hypothesis can therefore be discarded. In addition, potassium fluxes cannot have been set up to compensate an osmotic water uptake since we found a significant potassium release even during the lowest exercise intensity when little if any water movement took place.

Cell damage can be ruled out as a cause of increased plasma potassium concentration because repair takes a week or more (Newham, Jones & Clarkson, 1987) while these subjects exercise daily at high intensities. In addition, damaged cells would not be expected to take up potassium after exercise. Therefore, if cell damage was the cause of increased plasma potassium concentration, a steadily increasing potassium concentration should be seen in series 3. We also conclude that

the fluctuations in plasma potassium concentration cannot be due to exchanges between plasma and red blood cells since separate control experiments showed no change in red blood cell potassium content during exercise (Vøllestad & Sejersted, 1989). Moreover, Juel *et al.* (1989) recently showed that a 1·8 mmol l^{-1} (2%) increase in potassium concentration of red blood cells post-exercise was due to a 2% reduction in the red cell volume, leaving the potassium content constant.

Considering that (1) the arterial samples were obtained 5–10 s after the end of exercise and (2) the circulation time from muscle to the arterial sampling site is of similar magnitude, our measured peak values are probably close to a true maximum. Moreover, similar post-exercise concentrations have been reported in the horse (Harris & Snow, 1986) and greyhounds (Fedde, Toll & Pieschl, 1989), and *in situ* recordings by potassium electrodes have not given higher values (Sejersted & Hallén, 1987).

Comparisons of changes in plasma potassium concentration to a simple model

Post-exercise elimination

Three features of the changes in plasma potassium concentration after exercise are important. First, the potassium concentration fell exponentially with a half-time of 25 s. It was the same for different experiments and differed little between subjects. This very rapid fall has been observed by others (Hirche *et al.* 1980; Fedde *et al.* 1989; Juel *et al.* 1989), but has also in previous years escaped attention, leading to erroneous conclusions about the effects of exercise on plasma potassium (Felig, Johnson, Levitt, Cunningham, Keefe & Boglioli, 1982).

There is convincing evidence that potassium is taken up by the muscles that have exercised (Hirche *et al.* 1980). The electrochemical force for potassium is directed out of the cell at rest, and this is probably the case immediately after exercise too. Thus, potassium must be transported by the Na^+–K^+ pump itself or by some carriers indirectly driven by the pump.

The exponential fall after exercise is compatible with a stepwise reduction of potassium efflux at the end of exercise combined with a reuptake rate which is proportional to the present plasma potassium concentration less its lowest value after exercise. This proportionality is one basic feature of the model described in the appendix. Figure 7 shows a good agreement to the data.

What is then the physiological explanation for the linear relation between the pump rate and the extracellular potassium concentration? Direct stimulation of the pump by extracellular potassium is of little importance since $K_{0.5}$ (half-saturation of extracellular potassium sites) is probably less than 1 mmol l^{-1} (Sejersted, 1988). This means that raising the extracellular potassium concentration from 4 to 8 mmol l^{-1} will increase the pump rate by only 10%. Furthermore, if extracellular potassium were the direct stimulus for increased pump activity, potassium would be rapidly taken up by all tissues, but there is no evidence for this. On the other hand, loss of cellular potassium from the exercising muscle is most likely proportional to cellular uptake of sodium (Juel, 1986). The pump rate increases almost linearly with sodium concentration within the normal range of intracellular sodium concentrations (Sejersted, Wasserstrom & Fozzard, 1988). Hence a direct proportionality between

change in extracellular potassium and the Na^+–K^+ pumping in the exercising muscle can be assumed. However, we do not know whether the change in intracellular sodium is of sufficient magnitude to explain the increment of pump rate in full.

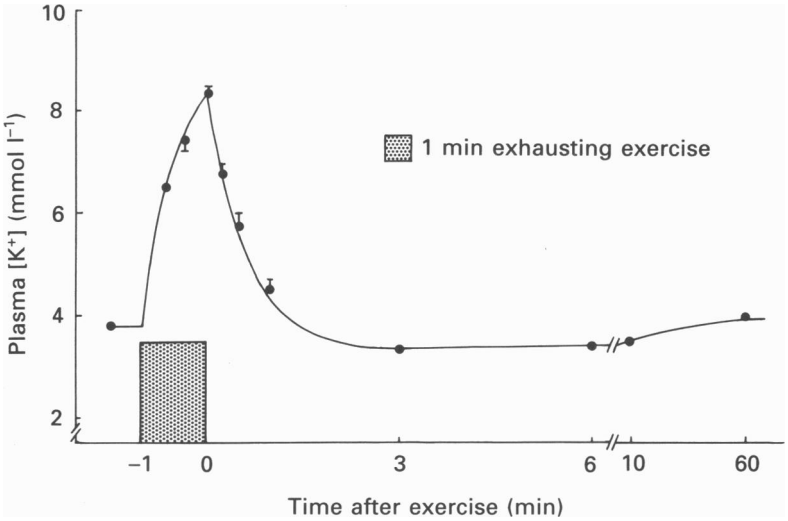

Fig. 7. Simulations of plasma potassium concentration during and after 1 min exhausting exercise. The curve is calculated assuming that from active muscle there is a stepwise increase (decrease) in potassium efflux above resting value at the onset (end) of exercise. As potassium accumulates extracellularly there is a reuptake (above resting value) proportional to the increase in extracellular potassium concentration. It is in addition assumed that exercise introduces a higher gain in the reuptake mechanism which causes an undershoot after exercise. This increase in the gain dies out with a time constant of 30 min. See the Appendix for further details. This means that the curve during exercise is described by eqn (3), while the curve from 0–3 min post-exercise is almost the same as described by eqn (2). The data are means ± S.E.M. ($n = 12$) and the same as in Fig. 1.

Post-exercise undershoot

The second important feature was the significant rebound of the plasma potassium concentration of 0·5 mmol l^{-1} below resting levels. This has also been seen for one-legged exercise in man (Juel *et al.* 1989) and in running greyhounds (Fedde *et al.* 1989). There may be three reasons for this rebound effect. First, during exercise, potassium may be distributed into more than one compartment. Plasma potassium may reach subnormal levels during reuptake by the exercised muscles due to a slower release from other compartments. However, constant infusion of potassium indicates that the time constant for reaching a new steady state is of the order of hours for resting experiments (Bia & DeFronzo, 1981). Redistribution to other compartments may therefore be of little importance in our experiments with short-lasting elevation of plasma potassium concentration. Second, potassium leaks out passively from resting cells, and this leakage may be reduced after exercise. However, we are not aware of any data supporting this possibility. Third, the reuptake mechanism may supercompensate so that more potassium is transiently taken up by the muscles

than was initially released. It has been shown that catecholamines and electric stimulation in itself increases the Na^+–K^+ pump rate (Everts, Retterstøl & Clausen, 1988), maybe by raising the pump's sensitivity to intracellular sodium (Ellingsen, Sejersted, Vengen & Ilebekk, 1989). Since intracellular sodium and plasma potassium concentrations may be linearly related, this would mean a steeper relationship between pump rate and plasma potassium concentration. Although we cannot exclude any of the three possibilities listed above, we hypothesize that the undershoot seen in the recovery is due to transient increased sensitivity of the Na^+–K^+ pump to intracellular sodium. This adequately describes the post-exercise undershoot (Fig. 7).

Increase during exercise

Both the data and the fitted curves from eqns (3) and (4) show that the plasma potassium concentration increased exponentially during exercise, which is the third feature of the model. This is compatible with a stepwise increase in potassium efflux at the onset of exercise gradually opposed by a reuptake which increases linearly with the plasma potassium concentration, as illustrated by the modelled curve in Fig. 7. Using the same time constant for rise and fall of potassium gave curves that fit the data well and is a consequence of the postulated tight relationship between loss of cellular potassium and Na^+–K^+ pump rate.

After 1 min of exhausting exercise the rate of rise was only 18% of the initial, and eqn (3) estimates a new steady-state value around 9 mmol l^{-1} if the 100% exercise could be continued for 3 min. This suggests that the reuptake mechanism has a sufficient pumping power to balance potassium release if it is stimulated adequately. That conclusion is in keeping with data of others showing that the Na^+–K^+ pump in human skeletal muscle has a pumping power of 75 μmol (kg wet weight muscle)$^{-1}$ s^{-1} (Nørgaard, Kjeldsen & Clausen, 1984). If maximally stimulated, the pump in 20 kg muscle could eliminate 90 mmol potassium in 1 min, which is somewhat more than our estimated gross efflux. It is therefore justified to conclude that the rise in plasma potassium concentration is due to an insufficient stimulation of the pump rather than a limited maximal power for pumping potassium.

We finally emphasize that reuptake of 80 mmol potassium requires around 40 mmol ATP. This is only 2% of the total energy release during 1 min running (Medbø & Sejersted, 1985), suggesting that the reuptake is not restricted by shortage of energy.

Consequences of extracellular potassium accumulation in muscle

During exercise there is a high blood flow through the exercising muscles. The diffusion coefficient of 2×10^{-9} m^2 s^{-1} (Hille, 1984) means that differences in the potassium concentration decays exponentially by diffusion with a half-time of less than 1 s over a distance of 100 μm. The large perfusion and the rapid diffusion means that the femoral–venous plasma potassium concentration must be close to the interstitial concentration.

A doubling of the extracellular potassium concentration to 8 mmol l^{-1} will depolarize the cell membrane by 18 mV (Nernst equation). A depolarization of this

magnitude may inactivate as many as 50% of the sodium channels (Hodgkin & Huxley, 1952). Potassium may therefore be an important cause of force loss leading to exhaustion (Bigland-Ritchie, Jones & Woods, 1979; Sejersted, Medbø & Hermansen, 1982). A drop in plasma potassium concentration to 3·3 mmol l^{-1} will hyperpolarize the cell membrane by around 5 mV. It is clear that both extremes of plasma potassium concentration may affect other organs, especially the heart.

In conclusion, our data suggest that there is sufficient capacity for reuptake of potassium in skeletal muscle to match increased release at least for intensities equal to or less than those leading to exhaustion in 1 min. The extracellular accumulation of potassium, which occurs at a decreasing rate as the exercise is continued, is therefore explicable in terms of a simple proportional regulator. Since the half-time of the system is 25 s, a new steady state cannot be reached when exhaustion occurs before 2–3 min. A possible role for extracellular potassium in contributing to exhaustion remains an intriguing possibility.

APPENDIX

A model describing fluctuations in plasma potassium concentration during exercise

The model, which comprises a simple proportional regulator (P-regulator), is based on the following assumptions: (1) Start (cessation) of exercise causes stepwise increase (decrease) in potassium efflux from muscle. (2) Potassium leaving the muscle cells is rapidly mixed within one compartment with constant volume. The almost equal concentrations in arterial and venous blood justifies this assumption, and the changes in plasma volume which do occur (Medbø & Sejersted, 1985, Sejersted *et al.* 1986) will have minor influence on the conclusions. (3) We introduce a compensating mechanism working as a P-regulator to account for the exponential time courses. A simple P-regulator can explain in full that higher (lower) steady-state levels are approached when passive outflow increases (decreases) during (after) exercise. On the other hand, it cannot account for the observed undershoot. (4) However, even at rest there is a passive potassium leak out from cells, and steady state at rest means that a passive outflow is balanced by a reuptake, probably driven by the Na^+–K^+ pump. A higher gain in the regulator will lower the steady-state level for a given passive outflow. We therefore introduce a higher gain in the P-regulator at the onset of exercise to account for the observed undershoot. (5) The undershoot persisted for at least 10 min after exercise, but it disappeared within 1 h. We accordingly assume that the increase in the gain dies out exponentially with a time constant of 30 min (half-time of 21 min). This model is illustrated in Fig. 7.

This regulator has no delay since it responds to the present state. However, in physiological terms there is a delay before the system reaches a new steady state. We also emphasize that the time constant of the system will be proportional to the extracellular distribution volume of potassium and inversely proportional to the muscle mass engaged and to the P-regulator's gain. Hence the time constant may vary by one order of magnitude or more between different experimental conditions.

As we have already pointed out, the undershoot may be due to redistribution of potassium to other tissue, lower passive outflow, or an increased sensitivity of the pump. All three possibilities can be simulated easily and fit the data well.

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